REMARKS

Claims 45, 46, 58, 59, 73, and 75-78 are pending in this application.[1] Claims 45, 46, 58, 59, 73, and 75-77 are rejected under 35 U.S.C. § 103(a) for obviousness over Relyveld (U.S. Patent No. 4,016,252; hereinafter "Relyveld") in combination with Antonucci et al. (U.S. Patent No. 5,508,342; hereinafter "Antonucci") and Gerhart et al. (U.S. Patent No. 5,085,861; hereinafter "Gerhart"). Claims 45, 46, 58, 59, 73, and 75-77 are also rejected for obviousness-type double patenting over claims 56 and 57 of U.S. Patent No. 6,541,037. By this reply, Applicant amends the specification and addresses each of the Office's rejections.

Amendment to the Specification

The present amendment to the specification corrects a typographical error in the cross-reference to related applications section set forth at the beginning of the application. In particular, the filing date provided for the priority application has been corrected. No new matter is added by the amendment.

Obviousness-Type Double Patenting Rejection

Claims 45, 46, 58, 59, 73, and 75-77 are rejected under the judicially-created doctrine of obviousness-type double patenting over claims 56 and 57 of U.S. Patent No. 6,541,037. In response to this rejection, Applicant submits a terminal disclaimer herewith, waiving the terminal portion of the term of the entire patent to be granted upon the above-identified application subsequent to the expiration date of U.S. Patent No. 6,541,037. In light of the terminal disclaimer, Applicant respectfully requests that the rejection of claims 45, 46, 58, 59, 73, and 75-77 for obviousness-type double patenting be withdrawn.

Rejection under 35 U.S.C. § 103(a)

Claims 45, 46, 58, 59, 73, and 75-77 are rejected under 35 U.S.C. § 103(a) for obviousness over the combination of Relyveld, Antonucci, and Gerhart. The Office states:

[1] The Office Action Summary inadvertently omitted claim 78, which was added with the Reply to Office Action filed on December 22, 2009.

> it would have been obvious to one of ordinary skill in the art at the time of invention to modify physical characteristics of Reyveld's [sic: Relyveld's] composition into an injectable paste, as suggested by Gerhard [sic: Gerhart] and Antonucci et al., and formulate a hardenable calcium phosphate formulation that is easily administered to a site of interest and readily dissolves in aqueous systems to form stable crystalline structures of HAP. One would be motivated to use an amorphous calcium phosphate in an injectable paste because the ordinary artisan would have had a reasonable expectation of success in achieving the same results of ease of administration to a site and readily dissolves in aqueous systems to form stable crystalline structures of HAP.

(Office Action, pp. 3-4.) For the reasons given below, Relyveld, Antonucci, and Gerhart, whether considered alone or in combination, fail to teach or suggest each and every limitation of present claims 45, 46, 58, 59, 73, and 75-78.

The Legal Standard for Determining Obviousness

Obviousness is a question of law based on underlying findings of fact. An analysis of obviousness must be based on several factual inquiries: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art at the time the invention was made; and (4) objective evidence of nonobviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). The Supreme Court reaffirmed this standard for obviousness in *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 82 U.S.P.Q.2d 1385 (2007). In this analysis, both the cited references and the invention must be considered as a whole (M.P.E.P. § 2141 (II)(B)). Obviousness must then be resolved on the basis of these factual determinations.

To support a *prima facie* case of obviousness, the Office must therefore make appropriate findings of fact and consider these facts in light of evidence provided by the Applicant. Furthermore, any obviousness rejection requires an analysis of the differences between the prior art and the claimed invention, as well as reasoning why one skilled in the art would bridge the gap between the two (M.P.E.P. § 2141 (III)). On this point, the Court states: "To facilitate review, this analysis should be made explicit. See *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) ('[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the

legal conclusion of obviousness')." *KSR Int'l Co.*, 550 U.S. at 418, 82 USPQ2d at 1396.

Furthermore, when making an obviousness determination, the Office must consider whether the prior art references, when combined, teach or suggest all of the claim limitations. M.P.E.P. 2143.03. See also *In re Wada and Murphy*, Appeal No 2007-3733 (January 14, 2008) (holding that "an examiner must make a 'searching comparison of the claimed invention – including all its limitations – with the teaching of the prior art'....Thus, 'obviousness requires a suggestion of all limitations in a claim.'") (citing *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003)).

The references cited by the Office do not establish a *prima facie* case of obviousness with respect to pending claims 45, 46, 58, 59, 73, and 75-78 because they fail to provide all the elements of the claimed invention. In particular, Relyveld, Antonucci, and Gerhart, alone or in combination, fail to teach or suggest a paste that hardens in an endothermic reaction into a poorly crystalline apatitic (PCA) calcium phosphate.

As is acknowledged by the Office, Relyveld describes only a gel formulation and fails to teach or suggest a paste formulation (see, e.g., p. 3 of the Office Action dated May 17, 2010 ("the present Office Action"), and p. 3 of the Office Action dated September 23, 2009). In addition, Relyveld fails to teach or suggest a delivery composition that includes amorphous calcium phosphate (ACP) or a poorly crystalline apatitic (PCA) calcium phosphate (p. 3 of the present Office Action) and that hardens in an endothermic reaction at body temperature. Relyveld also fails to teach or suggest that the gel composition hardens to form a PCA calcium phosphate. Instead, Relyveld states:

> the gel according to the invention has a chemical composition nearer to tricalcium phosphate $(PO_4)_2CA_3$...The overall chemical analysis carried out leads, for the phosphate of the gel, to a composition between those of dicalcium and tricalcium phosphates.

(Col. 2, lines 38-40, and col. 4, lines 4-6.)

In contrast to Relyveld's gel, the delivery composition of pending claims 45, 46, 58, 59, 73, and 75-78 is a paste formulation that hardens in an endothermic reaction at body temperature to form a PCA calcium phosphate. Relyveld fails to teach or suggest a delivery composition having any of these features. In addition, PCA calcium phosphate has a structure corresponding

to $CA_{10-x}(HPO_4)_x(PO_4)_{6-x}(OH)_{2-x}$ (see, e.g., Table 1 on p. 224, and p. 230 of Dorozhkin, *Materials* 2:221:291, 2009; and p. 11 of Combes et al., *Journal of Biomedical Materials Research,* Part A, 7:318-328, 2006), which is distinct from the calcium phosphate of Relyveld, which has a structure similar to $(PO_4)_2CA_3$ (see also ¶ 5 of the Declaration of Michael Strunk, Ph.D.; the "Strunk Declaration"). Thus, Relyveld fails to teach or suggest each and every limitation of pending independent claim 45, and claims dependent therefrom (see *In re Wada and Murphy, supra*).

To cure the deficiencies of Relyveld, the Office cites Antonucci for its disclosure of "amorphous calcium phosphate...[as the] preferred...mineralizing agent for the formation of HAP (hydroxyapatite)" (p. 3 of the present Office Action). Antonucci, however, fails to teach or suggest a PCA calcium phosphate, as is required by pending independent claim 45, and claims dependent therefrom. PCA calcium phosphate is distinct from HAP (see, e.g., Table 1 on p. 224, of Dorozhkin, *supra*), and thus Antonucci, like Relyveld, fails to teach or suggest this limitation of pending claims 45, 46, 58, 59, 73, and 75-78.

In addition, Antonucci describes the use of unsaturated monomers, such as "monomers having acrylate or methacrylate moieties" (see col. 8, lines 66-67), to form solid composites. Antonucci states that "[s]everal of the requirements of the unsaturated monomers employed are that they and the polymers which they form are relatively non-toxic and are capable of being quickly and easily cured at temperatures close to human body temperature" (col. 8, lines 48-52; emphasis added). Thus, Antonucci teaches only composites that harden in an exothermic curing reaction (see, e.g., ¶ 8 of the Strunk Declaration; see also BASF Corporation, "Arcylic Acid: A Summary of Safety and Handling," 3rd Edition; Atkinson and Grant, *J. Dent. Res.* 44:1040, 1965; Rohm and Hass Technical Bulletin (2006); Knets et al., *J. Achieve. Mater. Manuf. Eng.* 20:135-138, 2006; and Saltzman et al., *J. Orthop. Sports Phys. Ther.* 30:56-67, 2000; copies of which are provided). In contrast, the delivery composition of present claims 45, 46, 58, 59, 73, and 75-78 hardens in an endothermic reaction (see ¶¶ 6-8 of the Strunk Declaration). Thus, the combination of Relyveld and Antonucci fails to provide all the elements of the claimed invention.

Gerhart also fails to remedy the deficiencies of Relyveld and Antonucci. The Office cites Gerhart for its disclosure of "calcium phosphate containing compositions comprising biocompatible calcium phosphate ceramics that can be in the form of an injectable or moldable paste and [that] will solidify within 10 minutes after administration" (p. 3 of the present Office Action). Yet Gerhart, like Relyveld and Antonucci, fails to teach or suggest a composition that includes ACP or PCA, that is formulated as an injectable paste that hardens in an endothermic reaction at body temperature, and that forms a hardened PCA calcium phosphate. Thus, Gerhart, even if combined with Relyveld and Antonucci, fails to teach or suggest each and every limitation of pending claims 45, 46, 58, 59, 73, and 75-78 (*In re Wada and Murphy, supra*).

Gerhart describes a biodegradable cement composition that includes "particulate biocompatible calcium phosphate ceramics and a resorbable calcium salt dispersed in a cross-linked biodegradable polyester matrix" (see col. 4, lines 22-25). In particular, Gerhart states that the "'calcium phosphate ceramics'...refers to a number of sintered (heat-consolidated) materials...including not only tricalcium phosphate itself but also apatites, such as hydroxyapatite, and phosphorites" (col. 4, lines 61-66). Nowhere does Gerhart teach or suggest a composition that includes an ACP or PCA or that hardens to form a PCA calcium phosphate, as is required by pending independent claim 45, and claims dependent therefrom.

Furthermore, as was discussed in the Reply to Office Action dated December 22, 2009 (the "Second Reply"), Gerhart describes a bone cement that is cured in an *exothermic reaction.* In particular, Gerhart states:

> The present invention is directed to a biodegradable cement composition adapted for use in the surgical repair of living bone and for the controlled-release delivery of pharmaceutical agents. The composition comprises a particulate biocompatible calcium phosphate ceramic and a resorbable calcium salt dispersed in a cross-linked biodegradable polyester matrix.
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> *****
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> *The cross-linking reaction employed to "cure" the present composites is only mildly exothermic* compared to, for example, PMMA polymerization.

(Gerhart, col. 4, lines 19-25, and col. 8, lines 30-32; emphasis added.) In contrast, the composition of present claims 45, 46, 58, 59, 73, and 75-78 is formulated as an injectable paste that hardens in an endothermic reaction at body temperature.

As further evidence that Gerhart's composition is different from the composition of present claims 45, 46, 58, 59, 73, and 75-78, Applicant directs the Office to ¶¶ 6 and 7 of the Strunk Declaration, which presents additional data showing that the Gerhart composition hardens in an exothermic reaction having distinctly different energy kinetics when compared to a representative ACP composition prepared according to the methods of the present specification.[2] Thus, Gerhart, like Relyveld and Antonucci, fails to teach or suggest a composition that is formulated as an injectable paste that hardens in an endothermic reaction. Accordingly, Gerhart, whether considered alone or in combination with Relyveld and Antonucci, fails to teach or suggest a composition having each and every limitation of present claims 45, 46, 58, 59, 73, and 75-78.

For all the reasons given above, the combination of Relyveld, Antonucci, and Gerhart fails to teach or suggest a composition having each and every limitation of present claims 45, 46, 58, 59, 73, and 75-78. Furthermore, no combination of Relyveld, Antonucci, and Gerhart would achieve the composition of present claims 45, 46, 58, 59, 73, and 75-78 (see ¶ 4 of the Strunk Declaration). The rejection of claims 45, 46, 58, 59, 73, and 75-78 under 35 U.S.C. § 103(a) for obviousness over the combination of Relyveld, Antonucci, and Gerhart should be withdrawn.

[2] Applicant also directs the Office to the Declaration of Dr. Aliassghar N. Tofighi (the "Tofighi Declaration"), which was previously submitted in this application on December 22, 2009, and which is incorporated by reference herein. The Tofighi Declaration also addresses the exothermic characteristics of the Gerhart composition.

CONCLUSION

Applicant submits that present claims 45, 46, 58, 59, 73, and 75-78 are in condition for allowance, and such action is respectfully requested.

A petition to extend the period for replying for five (5) months, to and including June 17, 2011, is submitted herewith. Applicant authorizes the Office to deduct the fee required by 37 C.F.R. § 1.17(a) for the petition from Deposit Account No. 03-2095.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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